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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/789,081	ELLINGER ET AL.
	Examiner	Art Unit
	Robert T. Crow	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,52-58 and 62-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25,52-58 and 62-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 21 February 2007 in which claims 1-3, 5-8, 10-11, 13-14, 17-18, 20, and 22-25 were amended, claims 26-51 and 59-61 were canceled, and new claims 62-89 were added. All of the amendments have been thoroughly reviewed and entered.

The objection to the specification listed in the previous Office Action is maintained because the phrase " to spiking target molecule" appears to be a typographical error. The grammatically correct version appears to be "to spiking target molecules" as in claim 24. Appropriate correction is required.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 1-25, 52-58, and 62-89 are under prosecution.

Claim Amendments

2. Applicant's amendments to the claims fail to comply with 37 CFR 1.121. Claim 13 has deleted the text "a)" before formula 1 and "b)" before formula 2 by removing the text rather than striking though it. In addition, claim 22 has added a comma after the word "molecules" at the end of line 2 of the claim, but has not underlined the comma to indicate that the comma is new text.

3. It is emphasized that Applicant's response filed 21 February 2007 has been considered in the interest of customer service and compact prosecution. However, for the response to this Office Action to be complete, Applicant is **REQUIRED** to correct the errors listed above and file amendments that are compliant with 37 CFR 1.121. Failure to comply with this requirement will be considered **nonresponsive**.

Claim Objections

4. Claim 7 is objected to because of the following informalities: claim 7 recited the limitation "products of he" at the end of line 1 of the claim. This appears to be a typographical error. Appropriate correction is required.

Information Disclosure Statement

5. The Information Disclosure Statement filed 21 February 2007 is acknowledged. However, only the Abstract of Document WO 99/36827 is being considered because and English language translation of the remainder of the document has not been provided. Documents DE 19543232 and DE 19706570 are not being considered because no English language translation has been provided. The Non-Patent Literature documents have been considered but are lined through because no titles are provided. See 37 CFR 1.98.

Claim Rejections - 35 USC § 112 Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 62-86 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention

Claims 62-86 are indefinite in claim 62, which recites the limitation "in contact with a cleaving solution" at the end of claim 62. It is unclear how the first and second probe molecules have a selectively cleavable bond because said selectively cleavable bonds would no longer be present once contacted with a cleaving solution.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-16 and 87-89 are rejected under 35 U.S.C. 102(b) as being anticipated by Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000).

This is a new rejection necessitated by amendment.

Regarding claim 1, Koster et al teach a probe array. In a single exemplary embodiment, Koster et al teach an array surface in the form of DNA chip (column 4, lines 10-12 and Figure 3). Probe molecules are immobilized on the array surface; namely, capture sequence C is bound to spacer S on the surface of the DNA chip through the linkage L-L' (Figures 1 and 2 and column 5, line 45-column 6, line 36). The spacer S is a nucleic acid molecule (column 4, lines 60-62), as is capture sequence C (column 5, line 45-column 6, line 36). Sequence S and C are the instantly claimed first cleavage product of a first probe molecule. The immobilized probe also has a label in the form of mass modifying moiety M1 on sequence D2 (Figure 2), wherein D2 is a detector oligonucleotide and is the instantly claimed second cleavage product of the first probe molecule. Both of the fragments SC and M1-D1 of Figure 2 are bound to a target molecule at sequences TCS and TDS 1, respectively. Koster et al further teach the DNA chip allows for multiplex detection of multiple targets using different specific capture probes and multiple different defined sites (column 6, lines 35-50); thus, the array has other sequence fragments SC having different sequences and thus not bound to the probe. The other SC fragments are thus the cleavage products of the second probe molecule, and are similarly at their own defined sites on the DNA chip

Regarding claim 1, the courts have stated:

> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP§ 2113.

Thus, while Koster et al do not specifically teach the ends of the molecules are the result of a cleavage reaction, these limitations are part of the process of <u>making</u> the probe array rather than <u>structural</u> limitations of the probe array. Because Koster et al teach the <u>structural</u> elements of claim 1, the claim is anticipated by Koster et al.

Regarding claim 2-3, Koster et al teach the array of claim 1, wherein the first and second probe molecules are oligonucleotides; namely, the spacers S are nucleic acid molecules (column 4, lines 60-62), as are capture sequences C (column 5, line 45-column 6, line 36).

Regarding claim 4, Koster et al teach the array of claim 3, wherein the oligonucleotides are from 10 to 100 bases long; namely, the spacer S is 5 nucleotides long (column 12, lines 50-56) and the overhang on the target that is bound by the second cleavage product is 5 bases (column 47, lines 10-15);, thus the total length is 10 nucleotides.

Regarding claim 5, Koster et al teach the array of claim 1, wherein the cleavage products oar approximately equal in size; namely, Figure 2 shows TCS and TDS1 each having 8 bonds to their respective complementary cleavage products.

Regarding claim 6-14, Koster et al teach the array of claim 1. As noted above, even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. Thus, while Koster et al do not specifically teach the ends of the molecules are the result of a specific type of cleavage reaction, these limitations are part of the process of <u>making</u> the probe array rather than <u>structural</u> limitations of the probe array. Because Koster et al teach the <u>structural</u> elements of claim 1, the claim is anticipated by Koster et al.

Regarding claim 15, Koster et al teach the array of claim 1, wherein the label is a detectable unit; namely, the label M1 is a peptide (Figure 2 and column 15, lines 5-25). It is noted that claim 15 requires a label that is capable of detection by a labeled reporter probe, but does not actually require the labeled reporter probe to be hybridized for detection. Peptides are detectable by hybridization with a labeled reporter probe because signal generating antibodies to the peptide labels can be obtained. Thus, the peptide label of Koster et al meets the structural requirements of the claim

Regarding claim 16, Koster et al teach the array of claim 15, wherein the detectable unit is coupled through an anchor unit; namely, the peptide label is an oligoglycine molecule (column 15, lines 14-26). Page 40 of the specification does not provide limiting definition of an "anchor group" other than a group that <u>**can be**</u> detected by reaction with a specific binding component. The oligoglycine labels of Koster et al are detectable by labeled reporter probes because signal generating antibodies (i.e., labeled reporter probes) to the oligoglycine labels can be obtained. Thus, the oligoglycine label comprises a detectable label and an anchor group because the oligoglycine label of Koster et al can be detected by reaction with a specific binding component.

Regarding claim 87, Koster et al teach a probe array. In a single exemplary embodiment, Koster et al teach an array surface in the form of DNA chip (column 4, lines 10-12 and Figure 3). Probe molecules are immobilized on the array surface; namely, capture sequence C is bound to spacer S on the surface of the DNA chip through the linkage L-L' (Figures 1 and 3, column 6, lines 35-50, and column 5, line 45-column 6, line 4). The spacer S is a nucleic acid molecule (column 4, lines 60-62), as is capture sequence C (column 5, line 45-column 6, line 4). Linkage L-L' is the selectively cleavable disulfide linkage (column 13, lines 18-32). The immobilized probe also has a label in the form of mass modifying moiety M1 (Figure 3), which is a label in the form of a peptide (column 15, lines 5-25). The probe is immobilized at the 3' end via biotinylation (Example 9); thus, the 3' end is not expendable by the polymerase chain reaction. Koster et al further teach the DNA chip allows for multiplex detection of

multiple targets using different specific capture probes and multiple different defined sites (column 6, lines 35-50 and Figure 3).

Regarding claim 88, Koster et al teach the array of claim 87, wherein at least one probe is immobilized on the 3' end (Example 9).

Regarding claim 89, Koster et al teach the array of claim 87, wherein probe molecules of each of the multiple defined sites have at least one label, at least one selectively cleavable bond between the site of immobilization and the label, and lack a 3' OH group; namely, all of the probes have labels in the form of mass modifying moieties (Figure 3 and column 15, lines 5-25), cleavable links (column 13, lines 18-32), and are 3' immobilized (Example 9) because the probes are in a multiplex format (column 6, lines 35-50 and Figure 3).

10. It is noted that a prior art reference is considered as a whole and for all it stands for. Thus, while the rejections listed below present a modified interpretation of the teachings of the Monforte et al solely for the purpose of clarity, the rejections of the previously rejected claims are maintained for the reasons of record.

11. Claims 1-15, 62-76, 87 and 89 are rejected under 35 U.S.C. 102(b) as being anticipated by Monforte et al (U.S. Patent No. 5,700,642, issued 23 December 1997).

Regarding claim 1, Monforte et al teach a probe array for qualitative and/or quantitative detection of target molecules in a sample. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines 5-10). The primers in

the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the array is cleaved at a cleavable site within the immobilized probe while maintaining immobilization of the remaining fragments, which produces the second cleavage product of the first probe molecule and the cleavage product of the second probe molecule, both of which are still immobilized (column 16, lines 10-30 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

Regarding claims 2 and 3, Monforte et al teach the array of claim 1, wherein the first and second probes are oligonucleotides; namely, the probes are oligonucleotide primers (Abstract).

Regarding claim 4, Monforte et al teach the array of claim 3, wherein the oligonucleotides have a length of from 10 to 100 bases; namely, thirty nucleotides (column 8, line 66-column 9, line 3).

Regarding claim 5, Monforte et al teach the array of claim 1, wherein the first cleavage product of the first probe molecule and the second cleavage product of the first probe molecule are approximately the same size; namely, Figure 5A, wherein the first primer region is 5 nucleotides and the second regions in five nucleotides, with the cleavable linker in between (column 9, lines 10-40), and wherein the label is on the second region (column 9, lines 5-10). The broadly claimed limitation "approximately equal in

size" is interpreted to mean the cleavable linkage is in between the two ends due to the lack of explicit structural limitations on the number of bases or nucleotides in either cleavage product.

Regarding claim 6, Monforte et al teach the array of claim 1, wherein the cleavage products are products of non-enzymatic cleavage (column 7, line 51-column 8, line 3).

Regarding claim 7, Monforte et al teach the array of claim 1, wherein the cleavage products are products of chemical methods (column 7, lines 51-56).

Regarding claims 8 and 9, Monforte et al teach the array of claim 1, wherein the cleavage products are products of cleavage by the metal ions; namely, mercury ions (column 14, lines 20-22).

Regarding claim 10, Monforte et al teach the array of claim 1, wherein the cleavage products are products of cleavage by photolysis (column 7, lines 51-56).

Regarding claims 11-13, Monforte et al teach the array of claim 1, wherein the cleavage products are products of cleavage of a nucleic acid of the formula A1-S-A2, wherein S is a nucleic acid that comprises the at least one selectively cleavable bond and A1 and A2 are any nucleic acids of nucleic acid analogs; namely, the cleavable linker is a phosphorothioate within a nucleoside dimer (Figure 1I and column 11,lines 26-50).

Regarding claim 14, Monforte et al teach the array of claim 1, wherein the selectively cleavable bond is a phosphothioate (e.g., Figure 1H and column 11,lines 26-50).

Regarding claim 15, Monforte et al teach the array of claim 1, wherein the label is a detectable label and is fluorescent (column 9, lines 5-10). Fluorescent labels are detectable by labeled reporter probes because signal generating antibodies to the fluorescent labels can be obtained.

Regarding claim 62, Monforte et al teach a probe array. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and

the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines 5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the probe molecules are contacted with a cleaving solution (column 16, lines 20-25 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

Regarding claims 63 and 64, Monforte et al teach the array of claim 62, wherein the first and second probes are oligonucleotides; namely, the probes are oligonucleotide primers (Abstract).

Regarding claim 65, Monforte et al teach the array of claim 64, wherein the oligonucleotides have a length of from 10 to 100 bases; namely, thirty nucleotides (column 8, line 66-column 9, line 3).

Regarding claim 66, Monforte et al teach the array of claim 62, wherein the selectively cleavable bond is located approximately in the center between the site of the immobilization of the probe molecule and the label; namely, Figure 5A, wherein the first primer region is 5 nucleotides and the second regions in five nucleotides, with the cleavable linker in between (column 9, lines 10-40), and wherein the label is on the second region (column 9, lines 5-10). The broadly claimed limitation "approximately in the centre"

is interpreted to mean "in between" due to the lack of explicit structural limitations on the number of bases or nucleotides on either side of the cleavable bond.

Regarding claim 67, Monforte et al teach the array of claim 62, wherein the selectively cleavable bond cannot be selectively cleaved by enzymatic methods (column 7, line 51-column 8, line 3).

Regarding claim 68, Monforte et al teach the array of claim 62, wherein the selectively cleavable bond can be cleaved by chemical methods (column 7, lines 51-56).

Regarding claims 69 and 70, Monforte et al teach the array of claim 62, wherein the selectively cleavable bond can be selectively cleaved by the mercury ions (column 14, lines 20-22).

Regarding claim 71, Monforte et al teach the array of claim 62, wherein the selectively cleavable bond can be cleaved by photolysis (column 7, lines 51-56).

Regarding claims 72-74, Monforte et al teach the array of claim 62, wherein the probe molecules comprise a nucleic acid of the formula A1-S-A2, wherein S is a nucleic acid that comprises the at least one selectively cleavable bond and A1 and A2 are any nucleic acids of nucleic acid analogs (e.g., the cleavable linker is a phosphorothioate within a nucleoside dimer, Figure 1I and column 11,lines 26-50).

Regarding claim 75, Monforte et al teach the array of claim 62, wherein the selectively cleavable bond is a phosphothioate (e.g., Figure 1H and column 11,lines 26-50).

Regarding claim 76, Monforte et al teach the array of claim 62, wherein the label is a detectable label and is fluorescent (column 9, lines 5-10). Fluorescent labels are detectable by labeled reporter probes because signal generating antibodies to the fluorescent labels can be obtained.

Regarding claim 87, Monforte et al teach a probe array. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines

5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. Monforte et al further teach the array is used in a multiplex situation (column 27, lines 3-10), wherein multiple distinct targets are bound to multiple distinct probes on the array. Thus, at least two probes have targets bound.

Monforte et al further teach the target bound probes are extended in the presence of dideoxynucleotides (column 5, line 60-column 6, line 2). Extension with dideoxynucleotides results in probe not having 3' OH groups. Monforte et al further teach the array is used in a multiplex situation (column 27, lines 3-10), wherein multiple distinct targets are bound to multiple distinct probes on the array.

Regarding claim 89, Monforte et al teach the probe array of claim 87, wherein probe molecule of each of the defined sites have at least one label, at least one selectively cleavable bond between the site of immobilization and the label, and lack a 3' OH group; namely, all of the probes have labels (column 9, lines 5-10), cleavable links (column 27, lines 10-26), and are extended with dideoxynucleotides in the multiplex extension assay (column 27, lines 3-10).

Response to Arguments

Applicant's arguments filed 21 February 2007 have been fully considered but they are not persuasive for the reason(s) listed below.

Applicant argues on page 15 of the Remarks that because Monforte et al teaches a washing step before cleavage, that immobilized primer is single stranded at the time of cleavage, and thus no longer

has a target bound to the first and second cleavage products at the first and second regions of the target molecule.

However, as noted above, while Figure 6B of Monforte et al shows a single embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

In addition, while not relied upon in the rejections above, Monforte et al teach the wash solution is generally pure water at room temperature (column 16, lines 15-20). Washing with pure water at room temperature would not result in removal of the target DNA; thus, even with a washing step, the target would still be present.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the

examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. As noted above, a prior art reference is considered as a whole and for all it stands for. Thus, while the rejections listed below present a modified interpretation of the teachings of the prior art solely for the purpose of clarity, the rejections of the previously rejected claims are maintained for the reasons of record.

15. Claims 1, 15-16, 62, and 76-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,700,642, issued 23 December 1997) in view of Fung et al (U.S. Patent No. 4,757,141, issued 12 July 1988).

Regarding claim 16, Monforte et al teach the probe array of claim 1 for qualitative and/or quantitative detection of target molecules in a sample. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines 5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the array is cleaved at a cleavable site within the

immobilized probe while maintaining immobilization of the remaining fragments, which produces the second cleavage product of the first probe molecule and the cleavage product of the second probe molecule, both of which are still immobilized (column 16, lines 10-30 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

While Monforte et al also teach the array of claim 15, wherein the label is a detectable label and is fluorescent (column 9, lines 5-10), Monforte et al are silent with respect to anchor groups.

However, Fung et al teach the attachment of labels to probe molecules (i.e., oligonucleotides) using anchor groups (i.e., linkers; Abstract) with the added advantage that the linkers attach the label using automated methods in high yield (i.e., 95%; column 2, lines 40-63 and Example IV).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array comprising labels of Monforte et al with the anchor groups (i.e., linkers) as taught by Fung et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would result in a probe array that is readily labeled using automated method in high yield as explicitly taught by Fung et al (column 2, lines 40-63 and Example IV).

Regarding claim 77, Monforte et al teach the probe array of claim 62. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array

surface and the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines 5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the probe molecules are contacted with a cleaving solution (column 16, lines 20-25 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

While Monforte et al also teach the array of claim 76, wherein the label is a detectable label and is fluorescent (column 9, lines 5-10), Monforte et al are silent with respect to anchor groups.

However, Fung et al teach the attachment of labels to probe molecules (i.e., oligonucleotides) using anchor groups (i.e., linkers; Abstract) with the added advantage that the linkers attach the label using automated methods in high yield (i.e., 95%; column 2, lines 40-63 and Example IV).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array comprising labels of Monforte et al with the anchor groups (i.e., linkers) as taught by Fung et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would result in

a probe array that is readily labeled using automated method in high yield as explicitly taught by Fung et al (column 2, lines 40-63 and Example IV).

Response to Arguments

Applicant argues on page 16 of the Remarks that Fung et al does not teach anchor groups that are reacted with specifically binding components which are detectable themselves or trigger a detectable reaction.

However, the prior art of Fung et al is only relied upon for the broad interpretation of the instantly claimed "anchor group" as a specific linkage between the detectable unit and the probe. Applicant's citation of page 40 of the specification does not provide limiting definition of an "anchor group" other than a group that **can be** detected by reaction with a specific binding component. The fluorescent labels of Monforte et al are detectable by labeled reporter probes because signal generating antibodies (i.e., labeled reporter probes) to the fluorescent labels can be obtained. A narrower interpretation of the "anchor group" as merely being a label that **can be** detected by reaction with a specific binding component would thus allow the instantly claims to be rejected and anticipated by 35 USC 102(b) as anticipated by, rather than obvious over, Monforte et al because the fluorescent labels of Monforte et al can be detected by reaction with a specific binding component.

In addition, the anchor group (i.e., linker) of Fung et al is also a group that **can be** detected by reaction with a specific binding component because linker of Fung et al is detectable by labeled reporter probes because signal generating antibodies (i.e., labeled reporter probes) to the linker can be obtained

In addition, in further response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., detection by hybridization with a labeled probe) are not recited in the rejected claim(s). The claims are directed to an **intended use** of the detectable unit and anchor group; i.e., binding of the anchor group by a labeled reporter probe. Monforte et al in view of Fung et al teach the **structural components** of the probe array as

outlined above, and the claim is therefore obvious over the teachings of the prior art. Any recitation of intended use does not impart any further structural limitation of on the claimed subject matter.

Thus, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

16. Claims 1, 17-18, 22-25, 62, 78-79, and 83-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,700,642, issued 23 December 1997) in view of Lockhart et al (U.S Patent No. 6,040,138, issued 21 March 2000).

Regarding claim 17, Monforte et al teach the probe array of claim 1 for qualitative and/or quantitative detection of target molecules in a sample. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array (column 9, lines 5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the array is cleaved at a cleavable site within the immobilized probe while maintaining immobilization of the remaining fragments, which produces the

second cleavage product of the first probe molecule and the cleavage product of the second probe molecule, both of which are still immobilized (column 16, lines 10-30 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

While Monforte et al teach labeled probes having cleavable linkers (column 9, lines 5-10), Monforte et al are silent with respect to third probe molecules.

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising a first probe molecule in the form of an oligonucleotide that hybridizes to a target (Abstract) and third (i.e., additional) probe molecules that have no selectively cleavable bond; namely, mismatch control probes, wherein the mismatch control probe is an immobilized oligonucleotide (i.e., an ordinary, non-cleavable oligonucleotide; column 3, lines 30-40) with the added advantage that the third probe molecule (i.e., the mismatch probe) allows measurement of the concentration of hybridized material (column 17, lines 23-27).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to have modified the array of Monforte et al with the additional third probes as taught by Lockhart et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing measurement of the concentration of hybridized material as explicitly taught by Lockhart et al (column 17, lines 23-27).

Regarding claim 18, the array of claim 17 is discussed above. Lockhart et al also teach the third probe molecules are oligonucleotides; namely, the mismatch probes correspond to oligonucleotide probes

(column 3, lines 30-40), which have defined sequences because the mismatch probes have deliberately selected sequences (column 7, lines 20-22).

Regarding claim 22, the array of claim 1 is discussed above. While claim 22 is drawn to fourth probe molecules, the claim does not require third probe molecules. The instantly claimed fourth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claim 1.

While Monforte et al teach labeled probes having cleavable linkers (column 9, lines 5-10), Monforte et al are silent with respect to fourth probe molecules which do not have affinity for targets.

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target; Abstract) and fourth (i.e., additional) probe molecules having no specific affinity to target molecules; namely, expression level control probes, which are arranged on at least one array element because the probes are on the array (column 3, lines 50-55). The fourth (i.e. additional) probes have the added advantage that the fourth probes allows measurement of the overall health and metabolic activity of a cell, which allows a user to identify whether or not the results of a hybridization assay are due to a change in the amount of a target as a result of a change in the gene being studied or if the results are due to the general state of health of the cells from which the sample was isolated (column 16, lines 34-54).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al with the additional fourth probes as taught by Lockhart et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of having a control for the overall health and metabolic activity of a cell, which aids in the interpretation of assay results, as explicitly taught by Lockhart et al (column 16, lines 34-54).

Regarding claim 23, the array of claim 22 is discussed above. Lockhart et al also teach the fourth probe molecules are having a defined sequence because the expression control probes are complementary to known genes (column 16, lines 55-61).

Regarding claim 24, the array of claim 1 is discussed above. While claim 24 is drawn to fifth probe molecules, the claim does not require fourth or third probe molecules. The instantly claimed fifth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claim 1.

While Monforte et al teach labeled probes having cleavable linkers (column 9, lines 5-10), Monforte et al are silent with respect to fifth probe molecules which have affinity for spiking molecules.

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target (Abstract) and fifth (i.e., additional) probe molecules having no specific affinity to target molecules in the form of normalization controls (column 3, lines 50-55) arranged on at least one array element (e.g., on any position on the array; column 16, lines 36-31). The fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample; namely, the normalization controls hybridized to reference oligonucleotides added to the sample (column 16, lines 1-4), which has the added advantage that the fifth probe molecule provides a control for variation is signals between arrays (column 16, lines 1-9)

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al with the additional fifth probes as taught by Lockhart et al et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of providing a control for variation is signals between arrays as explicitly taught by Lockhart et al (column 16, lines 1-9).

Regarding claim 25, the array of claim 24 is discussed above. Lockhart et al also teach array elements distributed over the entire surface of the array on which said fifth probe molecules are located;

namely, the normalization probes are at multiple positions throughout the array (column 16, lines 26-31). Lockhart et al also teach the fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample in sufficient concentration to lead to a clearly detectable signal because the normalization controls hybridized to reference oligonucleotides added to the sample so that a signal is obtained (column 16, lines 1-4). Monforte et al teach wherein probe molecules have at least one label (column 9, lines 5-10) and at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the probe that is releasable from the array (column 9, lines 5-10).

Regarding claim 78, Monforte et al teach the probe array of claim 62. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines 5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the probe molecules are contacted with a cleaving solution (column 16, lines 20-25 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the

array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

While Monforte et al teach labeled probes having cleavable linkers (column 9, lines 5-10), Monforte et al are silent with respect to third probe molecules.

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising a first probe molecule in the form of an oligonucleotide that hybridizes to a target (Abstract) and third (i.e., additional) probe molecules that are labeled and have no selectively cleavable bond; namely, mismatch control probes, wherein the mismatch control probe is an immobilized oligonucleotide (i.e., an ordinary, non-cleavable oligonucleotide; column 3, lines 30-40) with the added advantage that the third probe molecule (i.e., the mismatch probe) allows measurement of the concentration of hybridized material (column 17, lines 23-27).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to have modified the array of Monforte et al with the additional third probes as taught by Lockhart et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing measurement of the concentration of hybridized material as explicitly taught by Lockhart et al (column 17, lines 23-27).

Regarding claim 79, the array of claim 78 is discussed above. Lockhart et al also teach the third probe molecules are oligonucleotides; namely, the mismatch probes correspond to oligonucleotide probes (column 3, lines 30-40), which have defined sequences because the mismatch probes have deliberately selected sequences (column 7, lines 20-22).

Regarding claim 83, the array of claim 62 is discussed above. While claim 83 is drawn to fourth probe molecules, the claim does not require third probe molecules. The instantly claimed fourth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claim 1.

While Monforte et al teach labeled probes having cleavable linkers (column 9, lines 5-10), Monforte et al are silent with respect to fourth probe molecules which do not have affinity for targets.

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target; Abstract) and fourth (i.e., additional) probe molecules having no specific affinity to target molecules; namely, expression level control probes, which are arranged on at least one array element because the probes are on the array (column 3, lines 50-55). The fourth (i.e. additional) probes have the added advantage that the fourth probes allows measurement of the overall health and metabolic activity of a cell, which allows a user to identify whether or not the results of a hybridization assay are due to a change in the amount of a target as a result of a change in the gene being studied or if the results are due to the general state of health of the cells from which the sample was isolated (column 16, lines 34-54).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al with the additional fourth probes as taught by Lockhart et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of having a control for the overall health and metabolic activity of a cell, which aids in the interpretation of assay results, as explicitly taught by Lockhart et al (column 16, lines 34-54).

Regarding claim 84, the array of claim 83 is discussed above. Lockhart et al also teach the fourth probe molecules are having a defined sequence because the expression control probes are complementary to known genes (column 16, lines 55-61).

Regarding claim 85, the array of claim 62 is discussed above. While claim 24 is drawn to fifth probe molecules, the claim does not require fourth or third probe molecules. The instantly claimed fifth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claim 1.

While Monforte et al teach labeled probes having cleavable linkers (column 9, lines 5-10), Monforte et al are silent with respect to fifth probe molecules which have affinity for spiking molecules.

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target (Abstract) and fifth (i.e., additional) probe molecules having no specific affinity to target molecules in the form of normalization controls (column 3, lines 50-55) arranged on at least one array element (e.g., on any position on the array; column 16, lines 36-31). The fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample; namely, the normalization controls hybridized to reference oligonucleotides added to the sample (column 16, lines 1-4), which has the added advantage that the fifth probe molecule provides a control for variation is signals between arrays (column 16, lines 1-9)

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al with the additional fifth probes as taught by Lockhart et al et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of providing a control for variation is signals between arrays as explicitly taught by Lockhart et al (column 16, lines 1-9).

Regarding claim 86, the array of claim 85 is discussed above. Lockhart et al also teach array elements distributed over the entire surface of the array on which said fifth probe molecules are located; namely, the normalization probes are at multiple positions throughout the array (column 16, lines 26-31). Lockhart et al also teach the fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample in sufficient concentration to lead to a clearly detectable signal because the normalization controls hybridized to reference oligonucleotides added to the sample so that a signal is obtained (column 16, lines 1-4). Monforte et al teach wherein probe molecules have at least one label (column 9, lines 5-10) and at least one selectively cleavable bond between the site of their

immobilization on the array surface and the label; namely, the label is in a fragment of the probe that is releasable from the array (column 9, lines 5-10).

Response to Arguments

Applicant's arguments regarding the teachings of Lockhart et al have been fully considered but are not persuasive for the reasons listed below.

A. Applicant argues on pages 16-17 of the Remarks that Lockhart et al does not teach immobilized labeled probes.

Lockhart et al do in fact teach immobilized probes in the form of a high density array of oligonucleotide probes immobilized on a surface (Abstract). The examiner agrees that Lockhart does not teach the labeled probes are immobilized; however, Lockhart is relied upon solely for the additional third, fourth, and fifth probes of the array.

B. Applicant further argues on page 17 of the Remarks that the fourth (i.e., expression level control) probes bind to target molecules, whereas the claim is drawn to fourth probes that have no affinity to target molecules.

However, as indicated by Applicant on page 17 of the Remarks, the fourth probes of Lockhart et al bind constitutively expressed genes. These genes are not the target molecules; rather, they are other molecules used to judge the quality of the sample comprising the target nucleic acids as outlined above.

If Applicant intends to have a fourth probe that is incapable of binding <u>any</u> molecule, target or otherwise, the claims would then be rejected under 35 USC 112, second paragraph, because it would be unclear how a molecule could be a <u>probe</u> and yet be incapable of binding <u>any</u> molecule whatsoever.

17. Claims 1, 19, 62, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,700,642, issued 23 December 1997) in view of Mackay et al (U.S. Patent No. 4,874,492, issued 17 October 1989).

Regarding claim 19, Monforte et al teach the probe array of claim 1 for qualitative and/or quantitative detection of target molecules in a sample. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines 5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the array is cleaved at a cleavable site within the immobilized probe while maintaining immobilization of the remaining fragments, which produces the second cleavage product of the first probe molecule and the cleavage product of the second probe molecule, both of which are still immobilized (column 16, lines 10-30 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

Monforte et al are silent with respect to detectable units not labeled to probe molecules.

However, Mackay et al teach arrays of polynucleotides in the form of 2-D gels (column 6, lines 56-67) having detectable units that are not attached to probe molecules; namely, calibration chemicals (column 6, lines 56-67), which have the added advantage of acting as calibration standards (column 6, lines 56-67).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al with the detectable labels not attached to probes (i.e., calibration chemicals) as taught by Mackay et al et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having standardized calibration as explicitly taught by Mackay et al (column 6, lines 56-67).

Regarding claim 80, Monforte et al teach the probe array of claim 62. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines 5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the probe molecules are contacted with a cleaving solution (column 16, lines 20-25 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product.of the first probe.

Monforte et al are silent with respect to detectable units not labeled to probe molecules.

However, Mackay et al teach arrays of polynucleotides in the form of 2-D gels (column 6, lines 56-67) having detectable units that are not attached to probe molecules; namely, calibration chemicals (column 6, lines 56-67), which have the added advantage of acting as calibration standards (column 6, lines 56-67).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al with the detectable labels not attached to probes (i.e., calibration chemicals) as taught by Mackay et al et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having standardized calibration as explicitly taught by Mackay et al (column 6, lines 56-67).

Response to Arguments

Applicant's arguments regarding the teachings of Mackay have been fully considered but are not persuasive for the reasons listed below.

Applicant argues on page 18 of the Remarks that Mackay teaches visualization of spots that are mobile and thus not immobilized.

However, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., immobilized third

probes) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Claims 17 and 20 merely require the third probes be arranged on different array elements, not immobilized thereon. A cursory review of the specification reveals no limiting definition of the term "arranged." Thus, the claim has been given the broadest reasonable interpretation consistent with the specification (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

Furthermore, Monforte et al teach immobilized probes. The teachings of Mackay are relied upon solely for the detectable units no linked to a probe molecule.

In addition, a review of the specification reveals no limiting definition of "immobilized" wherein the immobilization is irreversible. The term "immobilized" is therefore broadly interpreted, in a manner consistent with the specification, as encased within a solid matrix; i.e., an electrophoretic gel

18. Claims 20 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,700,642, issued 23 December 1997) and Lockhart et al (U.S Patent No. 6,040,138, issued 21 March 2000) as applied to claims 17 and 78 above, and further in view of Kievits et al (U.S. Patent No. 5,770,360, issued 23 June 1998).

Regarding claims 20 and 81, the array of claims 17 and 78 are discussed above on pages 12-17. Neither Monforte et al nor Lockhart et al teach different degrees in labeling.

However, Kievits et al teach immobilized oligonucleotides comprising a plurality of different probes, wherein the additional (i.e., second) probe molecules are arranged on different array elements; namely, two different oligonucleotide probes are arranged in two different spots (column 5, lines 17-50). The probes are labeled differently (column 5, lines 32-37); therefore, the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Kievits et al teach the

differential labeling has the added advantage of allowing indication of whether a test result is positive or negative (column 5, lines 17-44), thereby excluding false negatives (column 2, lines 1-9).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al and Lockhart et al with the different degree of labeling as taught by Kievits et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted a probe array having the added advantage of allowing indication of whether a test result is positive or negative, thereby excluding false negatives, as explicitly taught by Kievits et al (column 2, lines 1-9 and column 5, lines 17-44).

Response to Arguments

Applicant's arguments regarding the teachings of Kievits et al have been fully considered but are not persuasive for the reasons listed below.

Applicant argues on page 19 of the Remarks that Kievits et al does not teach the limitation for which it is cited; i.e., different degrees of labeling.

However, Kievits et al does teach the probes are labeled differently (column 5, lines 32-37) because the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Applicant's citation of pages 58-59 of the specification does not constitute a limiting definition of different degrees of labeling because the citation reads:

> "...the probes **preferably** differ in their degree of labeling an a characteristic manner, **for example** with a defined mixture of labeled and unlabelled probes varying an the form of a dilution series.... "

Emphasis is added by the examiner to illustrate that the definition refers to a single embodiment that is **not limiting**. Thus, the claim has been given the broadest reasonable interpretation consistent with the specification.

19. Claims 21 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,700,642, issued 23 December 1997) and Mackay et al (U.S. Patent No. 4,874,492, issued 17 October 1989) as applied to claims 19 and 80 above, and further in view of Kievits et al (U.S. Patent No. 5,770,360, issued 23 June 1998).

Regarding claims 21 and 82, the array of claims 19 and 80 is discussed above on pages 20-22.

Neither Monforte et al nor Mackay et al teach different degrees in labeling.

However, Kievits et al teach immobilized oligonucleotides comprising a plurality of different probes, wherein the additional (i.e., second) probe molecules are arranged on different array elements; namely, two different oligonucleotide probes are arranged in two different spots (column 5, lines 17-50). The probes are labeled differently (column 5, lines 32-37); therefore, the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Kievits et al teach the differential labeling has the added advantage of allowing indication of whether a test result is positive or negative (column 5, lines 17-44), thereby excluding false negatives (column 2, lines 1-9).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al and Mackay et al with the different degree of labeling as taught by Kievits et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted a probe array having the added advantage of allowing indication of whether a test result is positive or negative, thereby excluding false negatives, as explicitly taught by Kievits et al (column 2, lines 1-9 and column 5, lines 17-44).

20. Claims 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,700,642, issued 23 December 1997) in view of the Stratagene Catalog (1998).

Regarding claim 52, Monforte et al teach the probe array of claim 1 for qualitative and/or quantitative detection of target molecules in a sample. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (Abstract and column 24, lines 57-60). The probe molecules have at least one label because the primers are labeled (column 9, lines 5-10), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array; column 9, lines 5-10). The primers in the array are thus a first probe molecule immobilized at a first defined site and a second probe molecule immobilized at a second defined site.

Monforte et al further teach Figure 6A-B, which shows a target molecule immobilized a first probe molecule bound to a target. Monforte et al teach the immobilization of the primers occurs before enzymatic extension (column 16, lines 10-20); thus, the first and second probes are immobilized on the array surface. The first probe has the target hybridized, and the second probe is an immobilized primer not bound to a target. Following the extension reaction, the array is cleaved at a cleavable site within the immobilized probe while maintaining immobilization of the remaining fragments, which produces the second cleavage product of the first probe molecule and the cleavage product of the second probe molecule, both of which are still immobilized (column 16, lines 10-30 and Figure 6B).

While Figure 6B shows an embodiment wherein the array is washed before cleavage, Monforte et al also teach the wash step is optional (column 4, lines 50-62). Thus, Monforte et al teach an embodiment lacking a washing step, wherein said embodiment results in the retention of the target molecule on the array, wherein a first region of the target molecule remains bound to the first cleavage product of the first probe and a second region of the target molecule remains bound to the second cleavage product of the first probe.

Monforte et al also teach reagents for the selective cleavage of the selectively cleavable bond in the probe molecules (e.g., mercuric chloride; column 14, lines 20-22); hybridization buffer (e.g., annealing buffer; column 15, lines 54-56); and washing buffer (column 16, lines 15-19). Monforte do not teach kits.

However, the Stratagene catalog (1988) teaches that kits provide the two services of assembling and premixing a variety of different reagents specifically for a defined set of experiments as well as providing quality control (page 39, column 1).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array and reagents of Monforte et al into a kit format as discussed in the Stratagene catalog with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of having a variety of assembled and premixed reagents specifically designed for a defined set of experiments as well as providing quality control as explicitly taught by the Stratagene catalog (page 39, column 1).

Regarding claims 53-54, the kit of claim 52 is discussed above. Monforte also teach heavy metal ions; namely, mercuric chloride (column 14, lines 20-22).

Regarding claim 55, the kit of claim 52 is discussed above. Monforte et al also teach a reaction chamber; namely, a Petri dish (column 32, line 28).

Regarding claim 56, the kit of claim 52 is discussed above. Monforte et al also teach a detection device; namely, a dual microchannel plate detector (column 34, line 1).

Regarding claim 57, the kit of claim 52 is discussed above. Monforte et al also teach a temperature control unit; namely, a thermocycler (column 22, line 39).

Regarding claim 58, the kit of claim 52 is discussed above. Monforte et al also teach the probe array is in the form of a highly integrated autonomous unit; namely, the array is synthesized on a support in the form of a matrix (column 24, lines 57-60) and the solid support is a slide (column 31, lines 8-9);

therefore, the array is integrated because the probes are attached to the slide, and autonomous because the slide exists independently.

Response to Arguments

Applicant's remaining arguments on pages 19-21 of the Remarks rely on arguments set forth to address the rejections of the claims as either anticipated by, or obvious over, the teachings of the prior art. These arguments are addressed above. Since the arguments were not persuasive, the remaining rejections of the claims are maintained.

Conclusion

21. No claim is allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

23. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER